Abstract

Background: Primary cardiovascular disease (CVD) leading to cardiac arrest, is a common cause for critical care admission globally. The risk of severe ischaemic brain injury or death is still considerable. Several factors are known to influence later functional outcome in comatose, adult out-of-hospital (OHCA) patients with return of spontaneous circulation (ROSC) and treated with modern post-resuscitation care. Targeted temperature management (TTM) is still recommended in international guidelines after cardiac arrest. Registries of TTM patients are a valuable source of data to facilitate comparison between groups of OHCA patients with different baseline characteristics and thereby identify which variables are important for outcome. It remains, however, challenging to accurately and reliably predict outcome in this heterogeneous group of patients. Although earlier studies have shown that patients' background factors, prehospital circumstances and arrest characteristics are strongly associated with outcome, none of these variables are taken into account in the current recommended multimodal neurological prognostication algorithm (ERC/ESICM) of cardiac arrest patients treated and observed in intensive care units (ICU).

Aim: 1) To analyse if varying levels of TTM after OHCA were associated with later functional outcome in an international observational registry (study I). **2)** To investigate which variables and clinical information that carry the most predictive information in an OHCA population (study II). **3)** To investigate if a supervised machine learning algorithm called artificial neural network (ANN) could create reliable predictions of outcome for comatose OHCA patients using variables available already on hospital admission (study II), and during the first 3 days of ICU observation, using cumulative added information including biomarkers of brain injury (study III). **4)** To compare the predictive performance of an ANN with another supervised machine learning model called XGBoost, and to investigate the generalisability of each model (study IV). **5)** To demonstrate the hazard of adjustment for SAPS 3 scores in outcome studies on temperature intervention (Letter to the Editor).

Methods: OHCA patients from the INTCAR 1.0 and 2.0-registries, and the TTM trial were included for data analysis. Background and prehospital data, clinical variables available on admission to hospital and cumulative information collected from the first three days of intesive care (including different levels of biomarkers for brain injury) were used. Logistic regression, as well as two supervised machine learning models (ANN and XGBoost), were used for the analyses. Patient outcome was the dichotomised Cerebral Performance Category scale (CPC) where CPC 1–2 denoted a good functional outcome and CPC 3–5 denoted a poor functional outcome, respectively.

Results: 1) There was no significant association between temperature and outcome (p=0.35) in OHCA patients included in INTCAR 2.0 **2)** ANN predicted outcome with an AUC of 0.89 using 54 clinical variables available on admission to hospital and outperformed a model based on logistic regression (p=0.029). **3)** Incorporating biomarkers such as NSE improved the AUROC over the first 3 days of intensvie care. When adding NFL the prognostic performance was excellent from day 1. **4)** ANN and XGB predicted outcome with equal performance (AUROC of 0.86) (p=0.64). Internal validation showed similar performance in both models, whereas external validation performed well, but with significantly lower precision (p=0.04). **5)** The temperature component used to calculate SAPS 3 score during the first hour following admission to intensive care, greatly influenced the predicted hospital mortality rate in a model of simulated cardiac arrest patients undergoing different levels of temperature intervention.

Conclusion: 1) No significant difference in outcome at hospital discharge was found in patients receiving lower- vs higher TTM, supporting the findings from the TTM trial. **2)** ANN predicted long-term functional outcome on hospital admission well and factors related to the prehospital setting carried most predictive information. **3)** Clinically accessible biomarkers (NSE) and research-grade biomarkers (NFL) increased the prognostic performance in our ANN. **4)** ANN and XGB performed equally well when predicting outcome at hospital discharge using early variables only. When externally validated, both models performed well, but with lower descrimination. **5)** TTM-adjusted severity scoring models would probably improve the assessment of mortality in TTM treated cardiac arrest patients.